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METHODS FOR SYNTHESIZING 2-CHLORO-9-(2-DEOXY-2-FLUORO-β-D-ARABINOFURANOSYL)-*9H*-PURIN-6-AMINE

Cross Reference to Related Applications

This application claims the priority filing date of U.S. Provisional Patent Application No. 60/183,422 filed on February 18, 2000.

Statement Regarding Federally Sponsored Research or Development

This invention was made with support under U.S. Government Grant No. P01CA 34200 awarded by the National Cancer Institute. The U.S. Government has certain non-commercial rights in the invention.

Field of the Invention

This invention relates generally to methods for synthesizing a chemotherapeutic agent that is useful in the treatment of various malignancies. More particularly, this invention relates to improved methods for synthesizing 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-*9H*-purin-6-amine wherein the anionic form of a 2-chloro-6-substituted-purine is reacted with a protected and activated 2-deoxy-2-fluoro-D-arabinofuranose followed by reacting with an appropriate base such as ammonia to provide 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-*9H*-purin-6-amine. The present invention also relates to novel intermediates used in synthesizing the 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-*9H*-purin-6-amine such as 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-6-alkoxy-*9H*-purines and certain 2-chloro-6-substituted-9-(2-deoxy-2-fluoro-3,5-diprotected-β-D-arabinofuranosyl)-*9H*-purines.

Background of the Invention

Clofarabine [2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9H-purin-6-amine] has exhibited cytotoxicity in mice inoculated with P388 leukemia. As reported by Montgomery et al., Synthesis and Biologic Activity of 2'-Fluoro-2-Halo Derivatives of 9-β-D--Arabinofuranosyladenine, *Journal of Medicinal Chemistry,* 1992, 35, pp. 397-401,

clofarabine provided a good increase in life span of mice inoculated with P388 leukemia. The 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-*9H*-purin-6-amine was the most effective compound in the tested system. In addition, this compound exhibited reduced cleavage *in vivo* of the glycosidic bond as compared to Fludarabine.

The reported method for synthesizing 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-*9H*-purin-6-amine comprises a procedure using 3-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide for the coupling with 2,6-dichloropurine, followed by an amination/deprotection sequence.(See Montgomery, et al., 9-(2-Deoxy-2-fluoro- β-D-arabinofuranosyl)guanine: A Metabolically Stable Cytotoxic Analogue of 2'-Deoxyguanosine, *Journal of Medicinal Chemistry*, 1986, 29, pp. 2389-2392; and Montgomery et al., Synthesis and Biologic Activity of 2'-Fluoro-2-halo Derivatives of 9- β-D-Arabinofuranosyladenine, *Journal of Medicinal Chemistry* , 1992, 35, pp. 397-401).

However, the reported method for synthesizing 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine resulted in low overall yields of product, typically in the range of about 13%. The described coupling reaction produced a mixture of nucleosides from which the desired 9- β intermediate was obtained in only 32% yield after careful chromatography. Direct amination/deprotection of this material gave the desired 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine , plus a partially benzoylated 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H-purin*-6-amine that required further base treatment. Pure 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine was obtained only after several recrystallizations to remove salts and residual benzamide.

Such inefficient reactions will inhibit the ability to commercially produce 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine. Thus, there is a need for an improved method for synthesizing 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine that results in increased yields and/or reduced process steps.

Summary of the Invention

One aspect of the present invention is to provide a relatively high-yield method of synthesizing 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine that comprises reacting the anionic form of a 2-chloro-6 substituted purine with a protected

and activated 2-deoxy-2-fluoro-D-arabinofuranose to provide a 2,6-dichloro-9-substituted purine nucleoside. That product is then reacted with an alkoxide to provide a 2-chloro-6-alkoxy purine nucleoside. That compound is then reacted with ammonia to provide 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine.

Another aspect of the present invention relates to a method for synthesizing 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine by reacting the anionic form of a 2-chloro-6-substituted-purine with a protected and activated 2-fluoro-2-deoxy-D-arabinofuranose to provide a reaction product comprising a purine nucleoside, followed by reacting the purine nucleoside with an appropriate base such as ammonia to provide 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine.

The present invention also relates to novel intermediates used in synthesizing the 2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-*9H*-purin-6-amine. These intermediates include 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-6-alkoxy-*9H*-purines and 2-chloro-6-substituted-9-(2-deoxy-2-fluoro-3,5-diprotected-β-D-arabinofuranosyl)-*9H*-purines wherein the 6-substituent is selected from the group selected from amino, protected amino groups, azido and alkoxy.

Other features and objects and advantages of the present invention will become apparent from a reading of the following description.

Brief Description of the Drawing

Fig. 1 is a schematic diagram of one embodiment of a reaction comprising a synthesis method of the present invention.

Fig. 2 is a schematic diagram of an alternative embodiment of another synthesis method according to the present invention.

Fig. 3 is a schematic diagram of an alternative embodiment of a further synthesis method according to the present invention.

Best and Various Modes for Carrying Out the Present Invention

Reference to Figure 1 illustrates one of the synthesis methods according to the present invention. This chemical reaction as illustrated in Figure 1 provides a convenient

process for preparing 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine(5)in three steps and has resulted in overall yields of about 44%.

For the first step, a protected and activated 2-deoxy-2-fluoro-D-arabinofuranose **2** is reacted with a 2-chloro-6-substituted purine **1** to provide a reaction product comprising a 9-substituted purine nucleoside **3**. In this embodiment of the present invention, the preferred group in the 6 position is a halogen.

The preferred 2-chloro-6-substituted purine in the anionic form employed in this reaction scheme is 2,6-dichloropurine. Examples of suitable anionic forms include alkali metal salts, and organic amine salts. Alkali metal salts include sodium, potassium, and lithium salts. The metal salts can be obtained from metal hydrides such as NaH, KH and LiH or alkoxides such as $NaOCH_3$ and $KOCH_3$.

Organic bases for forming amine salts include hindered strong amine bases such as DBU(1,8-diazabicyclo [5.4.0] undec-7-ene);DBN (1,5-diazabicyclo [4.3.0]non-5-ene); Dabco (1,4-diazabicyclo [2.2.2] octane); and N,N-diisopropylethylamine.

A preferred anionic form is the sodium salt. The anionic form is needed to achieve the desired coupling reaction.

The 2-deoxy-2-fluoro-D-arabinofuranose contains protecting groups on the 3- and 5- hydroxyl groups and an activating group in the C-1 position.

Hydroxy protecting groups known in the art are described in Chapter 3 of the *Protective Groups in Organic Chemistry*, McOmie Ed., Plentum Press, New York (1973), and Chapter 2 of *Protective Groups in Organic Synthesis*, Greene, T., John Wiley and Sons, New York (1981and 1999); disclosures of which are incorporated herein by reference. Suitable protecting groups for the hydroxyl groups include ester forming groups, carbonates, alkyl ethers, aryl ethers, silyl ethers and carbonates. Examples of suitable esters are formyl, acetyl, substituted acetyl, propionyl, butynyl, pivaloyl, 2-chloroacetyl, benzoyl, substituted benzoyl, phenoxycarbonyl, methoxyacetyl and toluoyl.

Examples of carbonate derivates are phenoxycarbonyl, ethoxycarbonyl, butoxycarbonyl, vinyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl and benzyloxycarbonyl.

Examples of alkyl ether and aryl ether forming groups are benzyl, p-chlorobenzyl, diphenylmethyl, triphenylmethyl, t-butyl, methoxymethyl, tetrahydropyranyl, allyl, tetrahydrothienyl, 2-methoxyethoxymethyl.

Examples of silyl ether forming groups are trialkysilyl, trimethylsilyl, isopropyldialkylsilyl, alkyldiisopropylsilyl, triisopropylsilyl, t-butyldialkylsilyl and 1,1,3,3-tetraisopropyldisiloxanyl.

Examples of carbamates are N-phenylcarbamate and N-imidazoylcarbamate.

Mixtures of protecting groups can be employed if desired. For example, the 2-deoxy-2-fluoro-D-arabinofuranose **2** may have either two acyl groups, two ether groups, or combinations of acyl and ether groups.

Examples of activating groups for the C-1 of the carbohydrate include halogen such as Cl, Br and F; alkylsulfonyloxy, substituted alkylsulfonyloxy; arylsulfonyloxy, and substituted arylsulfonyloxy.

Suitable alkyl substituents contain 1- 8 carbon atoms and more typically 1-4 carbon atoms such as methyl, ethyl and propyl. A suitable aryl group includes phenyl.

Examples of alkyl- and substituted alkyl-sulfonyloxy groups are methanesulfonyloxy and 2-chloroethanesulfonyloxy.

Examples of aryl- and substituted aryl-sulfonyloxy groups are benzenesulfonyloxy, toluenesulfonyloxy, p-nitrobenzenesulfonyloxy and p-bromobenzenesulfonyloxy; while most preferred is methanesulfonyloxy.

A preferred protecting group is benzoyl and a preferred activating group is bromine. A specific compound that may be used as sugar compound **2** is 2-deoxy-2-fluoro-3,5-di-O-benzoyl-α-D-arabinofuranosyl bromide as prepared by C.H. Tann, *et al.*, *J. Org. Chem.*, 1985, 50, 3644-3647; the disclosure of which is hereby incorporated by reference.

The purine and activated carbohydrate derivative are typically employed in approximately equivalent amounts or with an excess of the purine and more typically about 1:1 to about 3:1; preferably about 1:1 to about 1.5:1 and more preferably about 1:1 to about 1.2:1 of purine to activated carbohydrate derivative.

This step of the process is typically carried out at temperatures of about 0° to about 100°C, more typically about 20°C to about 70°C and preferably about 20 °C to about 40°C; and at normal atmospheric pressures. However, higher or lower pressures can be employed if desired. This step of the process typically takes about 3 to about 24 hours for completion.

The reaction of the above-described purine compound **1** with the arabinofuranose sugar **2** preferably takes place in the presence of a solvent. Such solvent may be a dipolar, aprotic solvent such as acetone, acetonitrile, dimethylformamide, dimethyl

sulfoxide, sulfolane, dimethylacetamide and ethers such as tetrahydrofuran, dioxane, and dimethoxyethane.

When the reaction of the purine **1** and arabinofuranose sugar **2** is complete, the reaction mixture may be filtered and the solvent may be evaporated until a foam is obtained. The foam may be purified on flash silica using isopropyl acetate/hexane or any other suitable solution as the eluent. The fractions containing the desired 9-β isomer may be combined and evaporated to a residue that may then be crystallized from ethanol to give the desired 9-substituted purine nucleoside **3**.

For the next step, the 9-substitued purine-nucleoside **3** is reacted with an alkoxide to provide the corresponding 2-chloro-6-alkoxy purine nucleoside **4**. The alkoxide is preferably an alkali metal alkoxide and most preferably sodium methoxide.

This step of the process is typically carried out at temperatures of about 0°C to about 100°C, more typically about 20°C to about 40°C, and at normal atmospheric pressures. Higher or lower pressures can be employed, if desired. This step of the process typically takes about 3 to about 24 hours for completion.

Moreover, this step of the process preferably takes place in the presence of a solvent, with a preferred solvent being an alcohol which corresponds to the alkoxide used in the reaction. Upon completion, the reaction mixture may be treated with an ion exchange resin, filtered and evaporated to a residue. One commercially available ion exchange resin that has proved useful for this purpose is Dowex 50WX8-400 ion-exchange resin.

The desired 6-alkoxypurine nucleoside **4** may be derived from the residue obtained in this step by triturating the residue with hexane several times, followed by decantation of the supernatant liquor. The residue thus obtained may then be either recrystallized, or slurried in cold isopropyl alcohol in lieu of recrystallization, to give 6-alkoxypurine nucleoside **4**.

Finally, 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine (**5**) may be obtained by reacting the 6-alkoxypurine nucleoside **4** and ammonia.

This step of the process is typically carried out at temperatures of about 20°C to about 120°C and more typically about 70°C to about 100°C; and typically at pressures generated in a sealed vessel at the above temperatures. This step of the process typically takes about 12 hours to about 24 hours for completion.

This step of the process can be carried out in the presence of an alcoholic solvent such as methanol or ethanol or in the absence of a solvent.

The ammonia is typically present as an alcoholic solution such as in methanol or ethanol (typically saturated at 5°C). In a preferred embodiment, this reaction takes place in a stainless steel bomb at 80°C (65 psi). When the reaction is completed, the solvent may be removed and the residue dissolved in refluxing methanol, and preferably hot-filtered. Upon cooling, the crude product 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine **(5)** may be isolated by filtration. The product may be recrystallized from methanol to give high-quality -2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine **(5)**. Further recrystallizations of evaporated filtrates from methanol are optional to obtain additional 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine (5).

Reference to Figure 2 illustrates another reaction scheme according to the present invention for synthesizing 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine (5).

In the first step, a protected and activated 2-deoxy-2-fluoro-D-arabinofuranose **2** is reacted with the anionic form of a 2-chloro-6-substituted purine **1** to provide a reaction product comprising a 9-substituted purine nucleoside **3**. Examples of suitable substituents in the 6 position include groups such as amino, protected amino groups, azido and alkoxy, with amino being preferred. Suitable alkoxy groups are methoxy and ethoxy.

Suitable amino protecting groups are acyl, imino, and carbamates. Suitable acyl groups are acetyl-, benzoyl-, p-methoxybenzoyl, 2-methylbutryl- and pivaloyl.

A suitable imino group is dimethylaminomethylene.

Suitable carbamates are isobutyl-, t-butyl-, benzyl-, p-methoxybenzyl-, carbamates.

The preferred purine is the anionic form of 2-chloro-6-aminopurine. Examples of suitable anionic forms include alkali metal salts and organic amine salts as discussed above in the first embodiment of the present invention. Preferred anionic forms are the sodium salt and amine salts such as DBU.

The 2-deoxy-2-fluoro-D-arabinofuranosyl moiety contains protecting groups on the 3- and 5- hydroxyl groups and an activating group in the C-1 position.

Examples of suitable protecting groups and activating groups are those discussed above for the first embodiment according to the present invention.

A preferred protecting group is benzoyl and a preferred activating group is bromine.

A specific compound that may be used as the sugar reactant **2** is 2-deoxy-2-fluoro-3,5-di-O-benzoyl-2-α-D-arabinofuranosyl bromide.

The purine and the activated carbohydrate derivative are typically employed in approximately equivalent amounts or with an excess of the purine and more typically about 1:1 to about 3:1, preferably about 1:1 to about 1.5:1 and more preferably about 1:1 to about 1.2:1 of purine to the activated carbohydrate derivative.

This step of the process is typically carried out at temperatures of about 0°C to about 100°C, more typically about 20°C to about 70°C and preferably about 20°C to about 40°C; and at normal atmospheric pressures. However, higher or lower pressures can be employed if desired. This step of the process typically takes about 3 to about 96 hours for completion.

The reaction of the above-described purine compound **1** with the arabinofuranose sugar **2** preferably takes place in the presence of a solvent. Such solvent may be a dipolar, aprotic solvent such as acetone, acetonitrile, dimethylformamide, dimethyl sulfoxide, sulfolane, dimethylacetamide, and ethers such as tetrahydrofuran, dioxane and dimethoxyethane.

Upon completion of the reaction of the purine **1** and arabinofuranose sugar **2**, the reaction mixture may be filtered and the solvent may be evaporated until a foam is obtained. The foam may be purified on flash silica using isopropyl acetate/hexane or any other suitable solution of the eluent. The fractions containing the desired 9-β isomer may be combined and evaporated to a residue that may then be recrystallized from ethanol to give the desired 9-substituted purine nucleoside **3**.

When the group in the 6 position is amino or a protected amino group, the desired 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine (**5**) may be obtained by reacting the purine nucleoside **3** and a base such as ammonia and/or an alkali metal alkoxide such as sodium methoxide, an alkali metal carbonate such as sodium carbonate, and a alkali metal hydroxide such as lithium hydroxide. This step of the process with these groups is typically carried out at temperatures of about -20°C to about 80°C and more typically about 0°C to about 50°C; and typically at pressures generated in a sealed vessel at the above temperatures. This step of the process typically takes about 1 hour to about 24 hours for completion.

When the group in the 6 position is azido, the desired 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine(**5**) may be obtained by reacting the purine nucleoside **3A** with a reducing agent such as a hydrogenating agent to reduce the

azido group to an amino group and then reacting with a base as discussed above(see figure 3). The reducing step can be carried out, for instance, by reacting with hydrogen in the presence of a hydrogenation catalyst such as platinum or palladium. This step of the process is typically carried out at about normal room temperatures and a pressure of about 1 atm to about 3 atm. Moreover, when the group in the 6 position is azido, the order of the reaction steps can be reversed. In particular, the desired 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine(5) may also be obtained by reacting the purine nucleoside 3 with a base as discussed above and then reacting with a reducing agent to reduce the azido group to an amino group.

When the group in the 6 position is alkoxy, the desired 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine (5) may be obtained by reacting the purine nucleoside 3 with ammonia.

This step of the process is typically carried out at about normal room temperatures to about 120°C and more typically about 70°C to about 100°C; and typically at pressures generated in a sealed vessel at the above temperatures. This step of the process typically takes about 12 hours to about 24 hours for completion.

This step of the process is preferably carried out in the presence of an alcoholic solvent, such as methanol or ethanol or in the absence of a solvent.

Preferred embodiments for converting 3 to 5 include using ammonia or sodium methoxide. In the examples where the group (R in 3 in Fig. 2) is amino, protected amino such as acylamino, imino, and carbamate, one preferred embodiment is to use sodium methoxide at about 0°C to normal room temperatures. Alternatively, ammonia can be used.

The ammonia, when used, is typically present as an alcoholic solution such as in methanol or ethanol (typically saturated at 5°C). In a preferred embodiment, this reaction takes place in a stainless steel bomb at room temperature. When the reaction is completed, the solvent may be removed and the residue dissolved in refluxing methanol, and preferably hot-filtered. Upon cooling, the crude product 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine (5) may be isolated by filtration. The product may be recrystallized from methanol to give high-quality 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine (5). Further recrystallizations of the evaporated filtrates from methanol are optional to obtain additional 2-chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine (5).

One of ordinary skill in the art will readily see that some modification may be made to the preferred embodiments of the present invention set forth above. Further illustration of the present invention is set forth in the following examples, which are not to be construed as limiting the invention in any manner. The examples illustrate the individual steps of the above-described invention process.

Example 1

2,6-Dichloro-9-(2-deoxy-2-fluoro-3,5-di-O-benzoyl-β-D-arabinofuranosyl)-*9H*-purine*(3)* (Fig 1. R^1= Cl)

A suspension of 2,6-dichloropurine (4.0 g, 21.2 mmol) in anhydrous acetonitrile (130 ml) at room temperature was treated with NaH (916 mg of 60% in oil washed with heptane, 22.9 mmol), and the mixture was stirred 15 minutes under argon. To this stirred suspension, a solution of 2-deoxy-2-fluoro-3,5-di-*O*-benzoyl-α-D-arabinofuranosyl bromide (C.H. Tann, *et al., J. Org. Chem.*, 1985, 50, 3644-3647; 9g, 21.3 mmol) in acetonitrile (29ml) was added dropwise, and the mixture was stirred at room temperature overnight. Insoluble material was removed by filtration and washed with acetonitrile and chloroform. The combined filtrate and washings were evaporated to a near glass. A chloroform solution of this residue was applied to a flash column containing silica gel 60 (70-230 mesh, E. Merck). Elution with chloroform provided pure fractions that were combined and crystallized from boiling ethanol to give 1.6g (14%) pure product (HPLC, 100% 9-*β*). Material from less pure fractions was crystallized from chloroform at 5°C, 6.3 g(56%) (HPLC, 97% 9-*β*, 3% 9-α). After structure confirmation by 'H NMR, this material was used directly in the next step.

Example 2

2-Chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-6-methoxy-*9H*-purine(4)

2,6-Dichloro-9-(2-deoxy-2-fluoro-3,5-di-O-benzoyl-β-D-arabinofuranosyl)-*9H*-purine(3) (4.7g, 8.85 mmol) prepared as in Example 1 was suspended in anhydrous methanol (200ml) at room temperature. To this mixture, a 25 wt% solution of sodium methoxide in methanol (2.23 ml, 9.75 mmol) was added in one portion. After being stirred for 1.5 hours, the reaction became a clear solution. After 20 hours, the reaction was neutralized with a strong cation exchange resin (Dowex 50 X 4 [H^+]) which was collected after 15 minutes and washed with methanol. The combined filtrate was subjected to evaporation and was led to provide a gum that was triturated with two portions of petroleum ether 30-60 °C (decanted). The remaining material was dissolved

in hot 2-propanol (30ml)(filtered to clarity), and the solution was allowed to deposit crystals at room temperature before being chilled (5 °C) overnight. The product was collected, washed with ice-cold 2-propanol, and dried in vacuo to give the title compound, 1.7 g (60%), mp 199-200 °C (HPLC, 98%). Flash chromatography of the evaporated filtrate (silica gel 60, 70-230 mesh, E. Merck) with 95.5 chloroform-methanol as solvent provided additional material, 0.55 g(20%), mp 196-197 °C (HPLC, 96%).

Example 3

2-Chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-*9H*-purin-6-amine(**5**)

2-Chloro-9-(2-deoxy-2-fluoro- β-D-arabinofuranosyl)-6-methoxy-*9H*-purine(**4**) (6.2g, 19.5 mmol) prepared as in Example 2 was placed in a stainless steel pressure bomb with 300 ml ethanol saturated (0 °C) with anhydrous ammonia. The sealed vessel was heated at 80 °C for 16 hours. More ethanolic ammonia (30 ml) was added to the incomplete reaction, and heating was continued for 4 hours. The reaction solution containing a trace of starting material was evaporated to a white foam that crystallized from hot methanol (75 ml), 5.1 g. This relatively pure material was dissolved in refluxing methanol (110 ml), filtered, allowed to cool to room temperature, then chilled. Pure title compound was obtained in two crops, total 4.6 g (78%), mp 231 °C (HPLC, 99%).

Example 4

2-Chloro-9-(2-deoxy-2-fluoro-3,5-di-O-benzoyl- β-D-arabinofuranosyl)-*9H*-purin-6-amine (**3**) (Fig. 2, R=amino)

A suspension of 2-chloroadenine (21 mg, 0.12 mmol) in anhydrous acetonitrile (2.5 ml) at room temperature was treated dropwise with 98% DBU (18 μl, 0.12 mmol), and the mixture was stirred 25 minutes under argon. To this stirred suspension, a solution of 2-deoxy-2-fluoro-3,5-di-O-benzoyl- α-D-arabinofuranosyl bromide (**2**) (48 mg, 0.1 mmol) in acetonitrile (0.8 ml) was added dropwise. The mixture was stirred at room temperature until the 2-deoxy-2-fluoro-3,5-di-O-benzoyl- α-D-arabinofuranosyl bromide (**2**) was consumed. After 96 hours, insoluble material was removed by filtration and washed with $CHCl_3$. The combined filtrates were evaporated to a residue that was dissolved in $CHCl_3$. This solution was applied to a preparative layer silica gel plate (Analtech, 10 x 20 cm, 1, 000 microns) that was developed twice in 97:3 $CHCl_3$/MeOH. Product bands were extracted with 1:1 $CHCl_3$/MeOH, and the extracts were evaporated to give white solids, 16 mg (28%) (HPLC, 100% 9-β) and 20 mg (34%) (HPLC, 97% 9-α).

The above description and examples of the present invention are not intended to be limiting, and it is recognized that one of skill in the art will readily discern variations of this description, that are intended to be included within the spirit and scope of the invention.